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13. ABSTRACT (Maximum 200 words) Hypohydration is associated with orthostatic intolerance, however little is known about cerebrovascular mechanisms responsible. This study examined if hypohydration reduces cerebral blood flow velocity (CBFV) in response to an orthostatic challenge. Eight subjects completed four orthostatic challenges (temperate conditions) twice before (PRE-EU and PRE-HYP) and following recovery from passive heat stress (~3h @ 45oC, 50% rh, 1m/s air speed) with (POST-EU) or without (POST-HYP) fluid replacement of sweat losses (-3% body mass loss). Measurements included CBFV, mean arterial pressure (MAP), heart rate (HR), end-tidal CO2 (ETCO2), core (Tre) and skin (Tsk) temperatures. Test sessions included being seated (20 min) followed by standing (60 sec) then re-sitting (60 sec) with metronomic breathing (15 breaths/min). CBFV and MAP responses to standing were similar during PRE-EU and PRE-HYP. Standing POST-HYP exacerbated the magnitude ( $-28.0 \pm 1.4\%$ of baseline) and duration ( $9.0 \pm 1.6$ sec) of CBFV reductions, and increased cerebrovascular resistance (CVR) compared to POST-EU ( $-20.0 \pm 2.1\%$ and $6.6 \pm 0.9$ sec). Standing POST-EU also resulted in a reduction in CBFV, and a smaller decrease in CVR compared to PRE-EU. MAP decreases were similar for POST-EU ( $-18 \pm 4$ mmHg) and POST-HYP ( $-21 \pm 5$ mmHg) from seated to standing. These data demonstrate that despite similar MAP decreases, hypohydration and prior heat stress (despite apparent recovery) produce greater CBFV reduction when standing. These observations suggest that hypohydration and prior heat stress are associated with greater reductions in CBFV with greater CVR which likely contribute to orthostatic intolerance.				
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# Hypohydration and prior heat stress exacerbates decreases in cerebral blood flow velocity during standing

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**Carter, Robert III, Samuel N. Cheuvront, Carrie R. Vernieuw, and Michael N. Sawka.** Hypohydration and prior heat stress exacerbates decreases in cerebral blood flow velocity during standing. *J Appl Physiol* 101: 1744–1750, 2006. First published August 17, 2006; doi:10.1152/jappphysiol.00200.2006.—Hypohydration is associated with orthostatic intolerance; however, little is known about cerebrovascular mechanisms responsible. This study examined whether hypohydration reduces cerebral blood flow velocity (CBFV) in response to an orthostatic challenge. Eight subjects completed four orthostatic challenges (temperate conditions) twice before (Pre-EU and Pre-Hyp) and following recovery from passive heat stress (~3 h at 45°C, 50% relative humidity, 1 m/s air speed) with (Post-EU) or without (Post-Hyp) fluid replacement of sweat losses (~3% body mass loss). Measurements included CBFV, mean arterial pressure (MAP), heart rate (HR), end-tidal CO<sub>2</sub>, and core and skin temperatures. Test sessions included being seated (20 min) followed by standing (60 s) then resitting (60 s) with metronomic breathing (15 breaths/min). CBFV and MAP responses to standing were similar during Pre-EU and Pre-Hyp. Standing Post-Hyp exacerbated the magnitude ( $-28.0 \pm 1.4\%$  of baseline) and duration ( $9.0 \pm 1.6$  s) of CBFV reductions and increased cerebrovascular resistance (CVR) compared with Post-EU ( $-20.0 \pm 2.1\%$  and  $6.6 \pm 0.9$  s). Standing Post-EU also resulted in a reduction in CBFV, and a smaller decrease in CVR compared with Pre-EU. MAP decreases were similar for Post-EU ( $-18 \pm 4$  mmHg) and Post-Hyp ( $-21 \pm 5$  mmHg) from seated to standing. These data demonstrate that despite similar MAP decreases, hypohydration, and prior heat stress (despite apparent recovery) produce greater CBFV reduction when standing. These observations suggest that hypohydration and prior heat stress are associated with greater reductions in CBFV with greater CVR, which likely contribute to orthostatic intolerance.

fluid balance; dehydration; brain blood flow; hypotension

OVER ONE MILLION PATIENTS are admitted annually to hospitals for dizziness and syncope (32) that often results from orthostatic intolerance (16, 19). When a standing posture is assumed, blood is displaced from the thorax to dependent regions of the body (i.e., lower extremities; 32), which leads to transient reductions in cardiac output, cerebral perfusion pressure, and cerebral blood flow (31). The mean arterial pressure (MAP) reductions are minimized due to baroreceptor-mediated compensatory vasoconstriction in vascular beds (23). Physiological mechanisms responsible for the transient decreases in cerebral blood flow while better sustaining MAP are unclear. In addition, these observations appear contrary to the siphon model of sustained cerebral perfusion pressure and cerebral blood flow despite systemic hypotension (7). Dawson and

colleagues (7) have challenged the effectiveness of the siphon model to counteract orthostatic challenges in humans.

Cerebral autoregulation may act as another mechanism to sustain cerebral perfusion in response to blood pressure changes (29). Ogoh and colleagues (21) recently demonstrated that middle cerebral artery blood flow velocity (CBFV) varies in response to pulse pressure and that cerebral autoregulation allows maintenance of cerebral circulation during exercise-induced blood pressure increases, but suggest that this mechanism may be challenged by rapid blood pressure reductions. Cerebral autoregulatory responses during orthostatic-mediated pulse pressure reductions are not well defined, but might include vasoconstriction (10, 11). Physiological mechanisms mediating orthostatic intolerance are complex and still unclear.

Body water deficits (hypohydration) are associated with orthostatic intolerance (5, 6). As a result, patients admitted for dizziness or syncope are often treated for body water deficits, but exactly how hypohydration mediates orthostatic intolerance remains unclear. Charkoudian and colleagues (2) demonstrated that even modest hypohydration (~1.6% of body wt) can blunt baroreceptor control of blood pressure. Those investigators also found that the hyperosmolality, which is often associated with hypohydration (14), somewhat counteracts this blunted baroreceptor control (1). To our knowledge, the effect of hypohydration (induced by heat stress) on CBFV responses during orthostatic stress has not been reported.

The primary purpose of this study was to examine whether or not heat stress induced hypohydration (compared with euhydration) would exacerbate CBFV reductions in response to standing. We hypothesized that hypohydration (compared with euhydration) would exacerbate CBFV reductions in response to standing. Since heat stress was used to induce hypohydration, the secondary purpose was to examine whether decreases in CBFV would be due, in part, to prior heat stress (with recovery and rehydration). We further hypothesized that prior heat stress would not lead to greater reductions in CBFV compared with pre-heat stress. In justification of our second hypothesis, a previous study demonstrated that mild to moderate passive whole body heat stress (warm core and skin) decreased CBFV (33); however, these heat stress effects on CBFV may not be expected to persist with the abatement of skin and core temperature elevations during prolonged recovery from heat stress.

## METHODS

**Subject selection.** Eight healthy volunteers (age =  $24 \pm 6$  yr, height =  $170 \pm 6$  cm, weight =  $72.9 \pm 11.1$  kg, body fat  $22 \pm 6\%$ )

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participated in this study and completed all phases of experimentation. Subjects (6 men, 2 women) were physically active and moderately fit ( $\dot{V}O_{2\text{peak}} = 48 \pm 9 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Subjects were provided informational briefings and gave voluntary and informed written consent to participate. Subjects were not taking any medication, were nonsmokers, and had no history of any cardiovascular, cerebrovascular, or respiratory diseases. Investigators adhered to AR 70–25 and USAMRMC Regulation 70–25 on the use of volunteers in research and the appropriate Institutional Review Boards approved this study.

**Protocol.** Experiments were conducted at the same time of day (pre- and post-orthostatic challenges at  $\sim 0700$  and  $\sim 1200$ , respectively) and women were tested in the follicular phase of their menstrual cycle to control for circadian and reproductive fluctuations in body temperature and plasma volume (27). In addition, morning body weights (Toledo 1D1 accuracy  $\pm 20 \text{ g}$ , Worthington, OH) were obtained during a 10-day period to establish normal individual day-to-day body weight variability (3).

Subjects then completed two orthostatic challenge sessions in counterbalanced order spaced by  $\sim 1 \text{ wk}$ . On the morning of each session, body mass was measured and a 10-ml venous blood sample was collected for serum osmolality determination using freeze point depression method (Block Scientific, Nutley, NJ). A standardized breakfast was provided. Subjects were then instrumented for the continuous measurement of blood pressure (BP), CBFV, heart rate (HR), skin temperature ( $T_{\text{sk}}$ ), rectal temperature ( $T_{\text{re}}$ ), and respiratory end tidal gases. After instrumentation, subjects completed the following orthostatic challenge trial (Pre) modified from Serrador and colleagues (26): 20 min of seated baseline, followed by 1 min of standing, and then 10 min of seated recovery (Fig. 1).

The orthostatic challenge trials were conducted in a temperate environment [ $22^\circ\text{C}$ ; 30% relative humidity (rh), 1 m/s air speed]. Thereafter, subjects sat in a hot room ( $45^\circ\text{C}$ , 50% rh, 1 m/s air speed) for 3 h with [euhydration (EU)] or without [hypohydration (Hyp)] fluid replacement. No water was provided during the Hyp sessions, but fluid was consumed ad libitum during the EU sessions. A 2-h recovery period followed in which volunteers had a cool shower, were given a small standardized snack (Fruitbar, 250 kcal, 200 ml water in Hyp sessions), and replaced any remaining fluid deficits (EU sessions only). The precise fluid deficit incurred was calculated from the acute change in body mass from pre- to post-heat exposure, corrected for snack, and expressed as a percentage of pre-heat exposure body mass. During the EU sessions, volunteers were rehydrated back to pre-heat exposure body mass before the start of Post testing. After the recovery period, each subject repeated the stand test (Post) as previously described. Therefore, each subject completed two orthostatic challenge sessions (with and without fluid replacement) with each including a Pre and Post trial, for a total of four trials (a Pre-EU, a Post-EU, Pre-Hyp, and a Post-Hyp challenge trial).

**Measurement of middle CBFV.** CBFV was obtained by transcranial Doppler (TCD), with a 2-MHz transducer fitted to a headband

(MARC500, Spencer Technologies, Nicolet Biomedical). CBFV was measured using the right middle cerebral artery (MCA) using TCD sonography (TCD: DWL Multidop X-2) through the temporal window. A headband (modification of the Welder TCD Fixation, Nicolet Biomedical) was used to hold the probe, ensuring optimal recording position and angle for the duration of the experiment. When the headband and probe were removed, device measurements and markings of the probe and headband position were made to allow for accurate and repeatable repositioning. An investigator and technical staff were present to evaluate signal quality of all recordings to ensure that the subject maintained upright head position and assist subject during postural changes. The mean velocity of the MCA was obtained from the integral of the maximal TCD frequency shifts over one beat divided by the corresponding beat interval and expressed in centimeters per second. Cerebral vascular resistance (CVR) was calculated by MAP/CBFV. Hyperventilation in response to standing lowers arterial carbon dioxide levels and may cause cerebral arteriolar constriction (29). We controlled for respiratory rate (15 breaths/min) by having the subject take breaths at metronome cadence through a mouthpiece with the nose occluded by a nose clip. The end-tidal expired gas was sampled continuously by a carbon dioxide  $\text{CO}_2$  analyzer (ParvoMedics TrueOne 2400 ParvoMedics, Sandy, UT).

**Measurement of HR and blood pressure.** Blood pressure and HR were measured continuously using finger photoplethysmography (Finapres, model 2300, Ohmeda, Englewood, CO) and a three-lead ECG, respectively. The finger photoplethysmography was maintained at heart level throughout the protocol, and values were verified regularly by automated sphygmomanometry on the contralateral arm. The ECG and blood pressure signals were collected and stored by using an automated data-acquisition system (LabView, National Instruments, Austin, TX). MAP is diastolic arterial pressure plus one-third (systolic arterial pressure minus diastolic arterial pressure).

**Measurement of core and skin temperatures.** Instrumentation included a skin temperature harness with thermistors (Concept Engineering, Old Saybrook, CT) located at four sites (forearm, chest, thigh, and calf). Mean  $T_{\text{sk}}$  was calculated using the equation:  $0.3 (T_{\text{chest}} + T_{\text{forearm}}) + 0.2 (T_{\text{thigh}} + T_{\text{calf}})$ . Rectal body temperature ( $T_{\text{re}}$ ) was measured continuously by a thermistor (Yellow Springs Instruments, Yellow Springs, OH) inserted 10 cm beyond the anal sphincter.

**Statistical analysis.** All data analyses were performed using Sigma Stat 2.2 (SPSS) statistical software and are presented as means  $\pm$  SD. Following tests for normality of distribution and equality of variances, treatment effects were analyzed using a two-way analysis of variance (trial  $\times$  time) or one-way analysis of variance (trial) with repeated measures. When appropriate, Tukey's honestly significant difference procedure was used to identify differences among means following significant main and/or interaction effects. Effect size estimates were derived from CBFV using conventional  $\alpha$  (0.05)- and  $\beta$  (0.20)-values. A study sample of eight was adequate to detect meaningful physio-

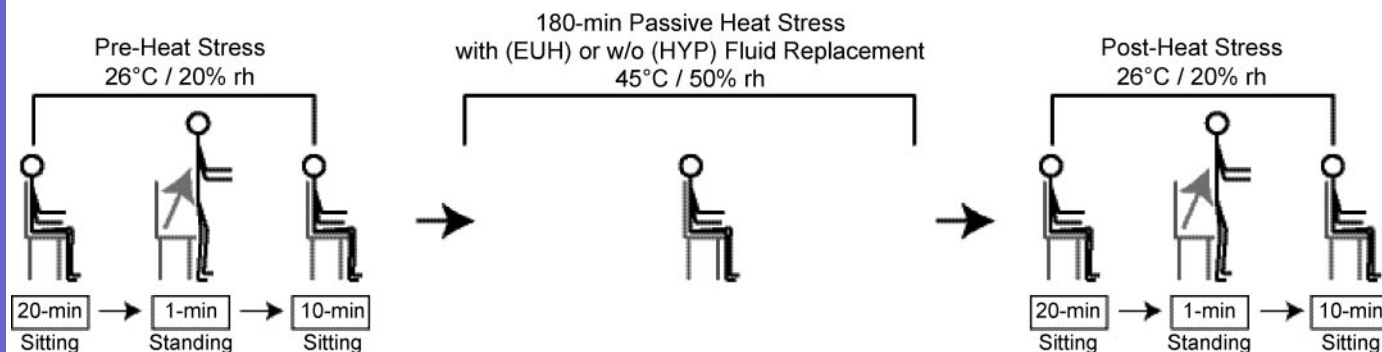


Fig. 1. Experimental design. EUH, euhydration; HYP, hypohydration; rh, relative humidity.



logical changes in CBFV, defined here as any value outside the 68% limits of agreement ( $\pm 1$  SD) for differences between repeated measures without perturbations.

## RESULTS

**Hydration assessment.** Euhydration was determined on the morning of each session by a body mass within 1% of the average 10-day baseline (3). Body mass in two subjects was 1% lower than 10-day baseline so they were given additional water with breakfast. Blood was drawn each morning to confirm euhydration using serum osmolality ( $289 \pm 1$  mosmol/kgH<sub>2</sub>O; range from 287 to 290 mosmol/kgH<sub>2</sub>O). The average fluid deficit was greater ( $P < 0.05$ ) Post-Hyp ( $-3.0 \pm 0.8\%$ , range from  $-2.7\%$  to  $-3.5\%$ ) than Post-EU ( $-0.3 \pm 0.7\%$ , range from 0.0 to  $-0.5\%$ ).

**Temperature and end-tidal CO<sub>2</sub> responses.** Table 1 provides the core temperature, skin temperature, and end-tidal carbon dioxide (ETCO<sub>2</sub>) responses. Prior to heat stress exposure (Pre),  $T_{re}$  values were similar for EU and Hypo sessions. No differences in  $T_{re}$  were found between Pre-EU and Post-EU. However,  $T_{re}$  was significantly higher during the Post-Hyp compared with the other trials. No differences were found between  $T_{sk}$  values obtained at any measurement time (Table 1). No differences were found between ETCO<sub>2</sub> values obtained at any measurement time (Table 1).

**Hemodynamic and CBFV responses.** CBFV and MAP demonstrated changes within the first 30 s after standing that were not captured in the mean values. Figure 2 demonstrates the changes in CBFV and MAP for a representative subject during the Post-EU and Post-Hyp trials. Note that baseline CBFV and MAP values (when seated) were immediately reduced to a nadir value that then rapidly returns to baseline values during the first 30 s of standing. Figure 3 presents mean data for the changes in CBFV in response to standing during the Pre-EU, the Post-EU, the Pre-Hyp, and Post-Hyp trials. Prior to heat stress exposure, similar CBFV responses were found for the Pre-EU and Pre-Hyp trials (Fig. 3A). CBFV decreased from baseline to nadir when standing (Fig. 3B). These CBFV decreases were larger during Post-EU than both Pre trials, and larger during Post-Hyp than both Pre trials and Post-EU. Figure 3 also shows the time from nadir to reestablishing baseline CBFV while still standing. This recovery time was longer ( $P < 0.05$ ) for Post-Hyp compared with Pre-Hyp, Pre-EU, and Post-EU. Figure 4 shows the MAP decreases from baseline to nadir during standing. Recovery time from standing MAP nadir (back to baseline) was similar for Post-Hyp ( $7.1 \pm 0.6$  s) and Post-EU ( $6.8 \pm 0.5$  s; Fig. 4). Baseline cerebrovas-

Table 1. Cerebral Blood Flow Velocity and Hydration Status

	Euhydration	Hypohydration
Tre (Pre)	$36.5 \pm 0.2$	$36.6 \pm 0.1$
Tre (Post)	$36.8 \pm 0.2$	$37.3 \pm 0.1^*$
Tsk (Pre)	$32.5 \pm 0.7$	$32.7 \pm 0.5$
Tsk (Post)	$32.8 \pm 0.8$	$32.4 \pm 0.6$
ETCO <sub>2</sub> (Pre)	$40.8 \pm 1.3$	$41.2 \pm 1.9$
ETCO <sub>2</sub> (Post)	$41.0 \pm 1.7$	$41.1 \pm 1.4$

Values are means  $\pm$  SD. Tre, rectal temperature ( $^{\circ}$ C); Tsk, skin temperature ( $^{\circ}$ C); ETCO<sub>2</sub>, end-tidal CO<sub>2</sub> (mmHg). \*Significant difference between hypohydration and euhydration conditions.

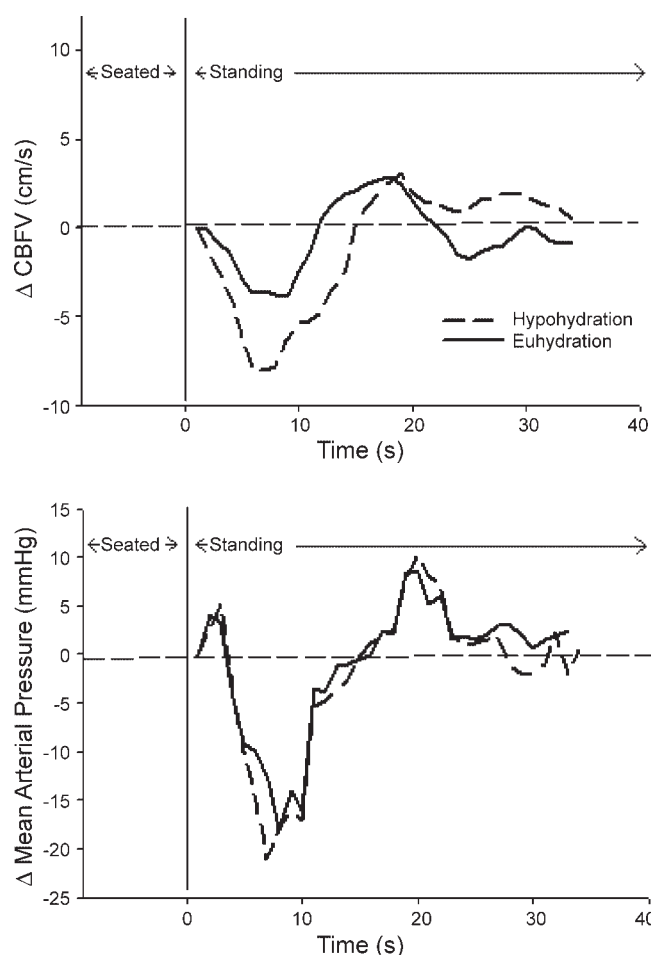


Fig. 2. Representative waveform of changes in middle cerebral blood flow velocity (CBFV) and mean arterial pressure (MAP) from one subject in response to standing while euhydrated (dashed line) and hypohydrated (solid line). Figure shows means  $\pm$  SD.

cular resistance was higher during Post-EU ( $1.75 \pm 0.21$  units) compared with Post-Hyp ( $1.60 \pm 0.13$  units) and baseline values (Pre-EU and Pre-Hyp,  $1.53 \pm 0.12$  units and  $1.59 \pm 0.15$  units, respectively). Figure 5 shows that CVR increased ( $P < 0.05$ ) in response to standing during the Post-Hyp trial, whereas during the other three conditions (Post-EU, Pre-EU, and Pre-Hyp) CVR decreased (Fig. 5).

Figure 6 provides mean values over time for CBFV, MAP, and HR responses during the four orthostatic challenge trials. These values represent the last 1 min of being seated before standing, the first and last 30 s of the 1-min stand, and the final minute of reassuming the seated position. MAP values were greater for Post-EU during seated baseline, during the first 30 s of standing, and during the second 30 s of standing compared with the same time periods in the other three trials. Mean heart rate was greater during the Post-Hyp at seated baseline, the first 30 s of standing, the second 30 s of standing, and Post seated recovery compared with Post-EU, Pre-EU, and Pre-Hyp trials.

## DISCUSSION

This is the first study to examine the effects of hypohydration and prior heat stress on CBFV responses to standing (orthostatic challenge). Our primary finding was that hypohy-

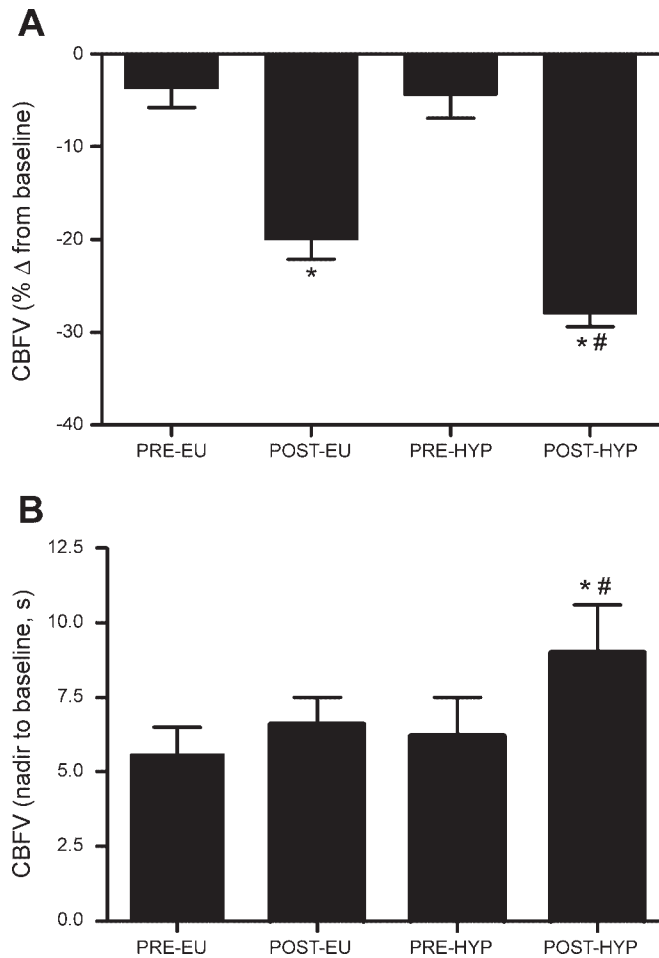


Fig. 3. A: %change from baseline in CBFV in response to standing in 4 states: pre-heat stress and euhydrated (Pre-Hyp or Pre-EU), post-heat stress and euhydrated (Post-EU), and post-heat stress and hypohydrated (Post-Hyp). B: time from nadir back to baseline CBFV (see Fig. 2 for changes in CBFV). \*Significant difference from Pre-EU and Pre-Hyp (control). #Significant difference from Post-EU. Figure shows means  $\pm$  SD.

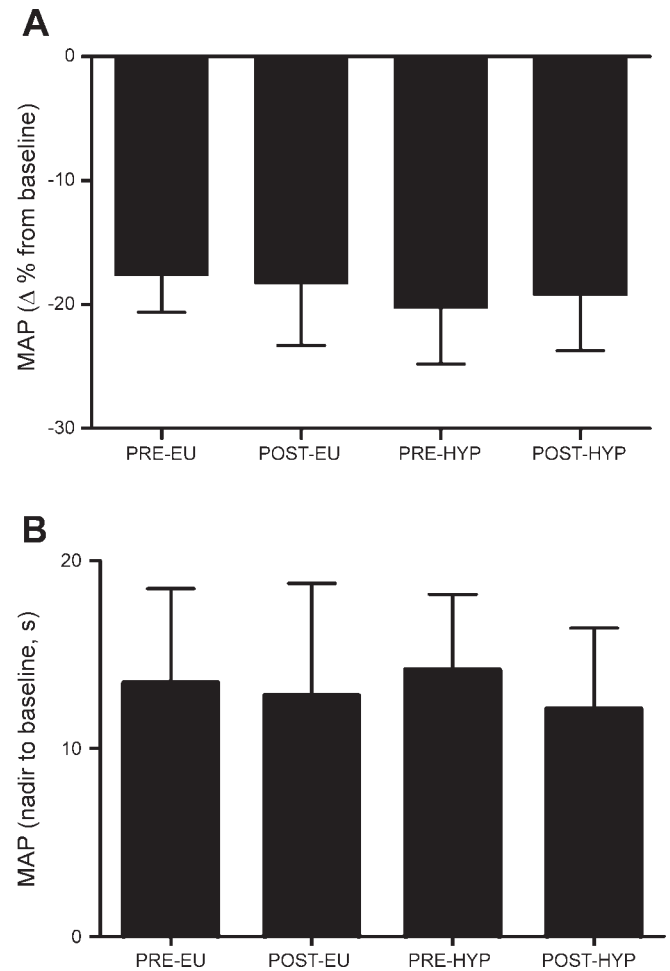


Fig. 4. %Change from baseline in MAP in response to standing: Pre-EU and Pre-Hyp, Post-EU, and Post-Hyp. Time from nadir back to baseline MAP (see Fig. 2 for changes in MAP). Figure shows means  $\pm$  SD.

dration exacerbated the magnitude and duration of CBFV reductions when standing. Our second finding was that prior heat stress (despite apparent recovery) also reduced CBFV when standing. These CBFV changes were also associated with altered cerebrovascular responses, but occur despite no difference in MAP responses to standing between trials.

We employed a water deficit corresponding to 3% of body mass because this magnitude of hypohydration is associated with reduced aerobic exercise performance and reduced orthostatic tolerance (14). Likewise, more modest body water deficits ( $\sim 1.6\%$  body mass loss) can blunt baroreceptor sensitivity (2). The body water deficit was fully replaced (as indicated by body weight) during recovery for the Post-EU trial. Sufficient time had passed ( $>3$  h) for the consumed fluids to be absorbed and re-equilibrated to the total body water (18); however, this was not documented by body water compartment measurements. We employed a repeated-measures design and care was taken to control for time of day and recovery from heat stress.

The cardiovascular responses we observed for the Pre standing trials were qualitatively similar to results previously reported (29, 31). Standing and other orthostatic challenges

provoke a transient reduction in blood pressure and CBFV and elevations in heart rate (29, 31). Displacement of central blood volume (1/2 to 1 liter of blood) to legs acts to reduce venous return with assumption of the upright position. During standing, tensing of the leg skeletal muscle attenuates decreases in central blood volume and the reduction in cerebral perfusion as

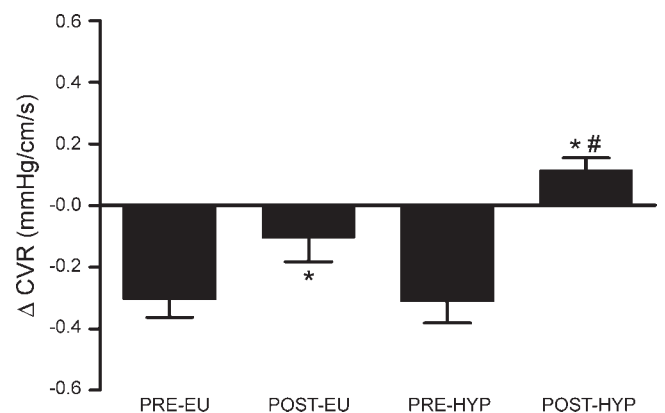


Fig. 5. Delta cerebral vascular resistance in response to standing: Pre-EU and Pre-Hyp, Post-EU, and Post-Hyp. \*Significant differences from Pre-EU and Pre-Hyp. #Significant differences from Post-EU. Figure shows means  $\pm$  SD.

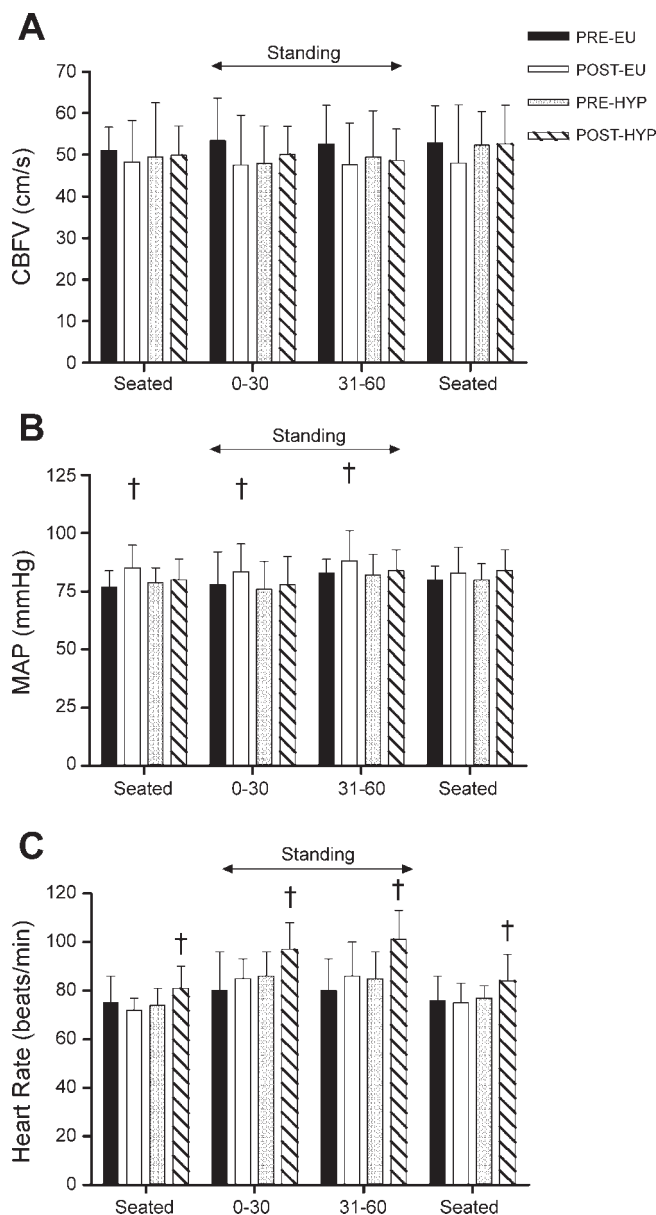


Fig. 6. CBFV, MAP, and heart rate (HR) during seated baseline, standing, and seated recovery before and after 3 h of passive heat stress with fluid (hypohydration) and without fluid restriction (euhydration). †Significant difference from all other trials. Figure shows means  $\pm$  SD.

well as stabilizes central circulatory variables and reduces sympathetic activity (31). In addition to these changes in body fluid, central blood volume is affected by transcapillary filtration of fluid into the interstitial spaces in response to the high capillary pressure with little interstitial counterpressure in the dependent parts of the body. Due to hydrostatic pressures, 5 min of standing has been shown to induce losses in excess of 0.5 liter of plasma water (17). These hydrostatic effects also affect end-diastolic filling of the right ventricle, contributing to reductions in stroke volume and cardiac output (12). However, compensatory vasoconstriction of resistance and capacitance vessels in inactive vascular beds (e.g., renal and skin), attenuates these decreases in cardiac output (22). These fluid shifts are associated with compensatory mechanisms including

baroreceptor-mediated cardiovascular adjustments and perhaps cerebral autoregulation (16).

The novelty of the experiment herein was the addition of hypohydration and prior heat stress to an orthostatic challenge. Hypohydration exacerbated the magnitude and duration of CBFV decrease to standing (Figs. 2 and 3, A and B), whereas prior heat stress also exacerbated the magnitude of the CBFV decrease to standing. Because systemic blood pressure reductions with standing were similar with Post-Hyp and Post-EU trials, the greater decrease in CBFV during the Post-Hyp was likely due, in part, to altered cerebral vascular responses. Indeed, cerebral vascular resistance (CVR) increased during the Post-Hyp trial and decreased by a smaller magnitude during the Post-EU trial. Possible mechanisms for increased CVR might include 1) altered autonomic neural control of the cerebral circulation due to unloading of low pressure baroreceptors (29, 34), 2) shifts in cerebrovascular autoregulation curve (i.e., greater reductions in CBFV per change in perfusion pressure; Ref. 33), and/or 3) decreased central blood volume independent of cerebral autoregulation (20). For the former mechanism, it is possible that prior heat stress may have mediated a continued increased sympathetic outflow during the subsequent recovery period and may help explain the increased CVR during Post-EU.

Doppler CBFV measures were used as a substitute for blood flow along with MAP to calculate CVR. CBFV is directly related to blood flow only if the diameter of the blood vessel remains constant. Actual perfusion pressure can be determined only if transcranial pressure, venous pressure, and MAP at the level of the brain are known (15), all of which are very difficult to measure in most human studies (9). The diameter of the middle cerebral artery likely only changes slightly with hematologic perturbations (8a, 8b). Therefore, Doppler measurements are widely used to estimate acute changes in cerebral perfusion (19).

Previous studies have examined relationships between fluid drinking, body water balance, and heat strain on orthostatic tolerance and do not provide clear insight into why CBFV was reduced Post-EU. Drinking water can improve cerebrovascular responses and orthostatic tolerance in euhydrated subjects (4, 25). In contrast, restoration of fluid deficits does not immediately restore baroreflex function and blood pressure responses related to reducing orthostatic intolerance (2). In our study, prior drinking with restoration of fluid deficits preserved blood pressure but not CBFV responses to standing.

Hyperthermia alone can mediate physiological responses consistent with degraded orthostatic tolerance. Wilson and colleagues (33) demonstrated that whole body heating ( $\sim 1^\circ\text{C}$  increase in core temperature and  $\sim 4^\circ\text{C}$  increase in skin temperature) decreased MAP and CBFV and increased CVR in response to lower body negative pressure (LBNP). With increasing levels of orthostatic stress (LBNP), those investigators observed that the decreases in CBFV were greater during heat stress, suggesting that the reserve to buffer further decreases in cerebral perfusion was altered. In our study, core temperature was slightly elevated ( $\sim 0.3^\circ\text{C}$  Pre-EU to Post-EU;  $\sim 0.7^\circ\text{C}$  Pre-Hyp to Post-Hyp; Table 1) with no differences in skin temperature. This slight core temperature elevation can be fully accounted for by expected circadian patterns (27) from Pre- to Post-EU and thus should be considered as normothermic. The Pre-Post Hyp core temperature elevation can be accounted for



by circadian pattern ( $0.3^{\circ}\text{C}$ ) and expected hypohydration ( $0.4^{\circ}\text{C}$ ) effects (24). It remains possible that core temperature elevation from hypohydration, in the absence of skin temperature elevations, could have contributed to CBFV. Again, another possibility is that prior heat stress may have mediated a continued increased sympathetic outflow during the subsequent recovery period, despite recovery of body temperatures, and mediated increased CVR during subsequent orthostatic challenges.

CBFV has also been examined in response to other orthostatic challenges (e.g., LNBP, body tilt) with other methods that alter body fluid compartments (28, 30). Acute and prolonged bed rest are associated with loss of fluid from all compartments occurring over time (8). Conditions of bed rest and passive heat stress, both of which alter cerebrovascular responses to orthostatic stress, can result in hyperosmotic hypovolemia. However, the methods and body fluid compartment changes are very different (13, 35).

Limitations of the study include 1) employing CBFV to estimate cerebral blood flow, 2) inability to control for circadian patterns in body temperature, and 3) inability to separate modest hyperthermic consequences of hypohydration at rest.

In summary, these data demonstrate that hypohydration and prior exercise heat strain exaggerated the CBFV reductions associated with standing. These exacerbated CBFV reductions occurred despite no difference in MAP reductions, suggesting that increased cerebral vascular resistance may contribute to orthostatic intolerance associated with hypohydration and prior heat stress.

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